Short Communication

Cigarette Smoking and Breast Cancer[1]

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Abstract

***A priori* hypotheses suggest that cigarette smoking could either increase or decrease breast cancer incidence. To clarify these competing hypotheses, we used data from a very large population-based breast cancer case-control study to investigate the impact of smoking on breast cancer risk.**

Breast cancer patients less than 75 years old were identified from statewide tumor registries in Wisconsin, Massachusetts, Maine, and New Hampshire; controls were randomly selected from driver's license lists (age less than 65) or lists of Medicare beneficiaries (age 65–74). Information on reproductive history, medical history, and personal habits including cigarette smoking was obtained by telephone interview. A total of 6,888 cases and 9,529 controls were interviewed.

There was virtually no relationship between current smoking and breast cancer risk (multivariate odds ratio, 1.00; 95% confidence interval, 0.92–1.09), and former smokers had a barely increased risk (odds ratio, 1.10; 95% confidence interval, 1.01–1.19). Similar results were observed among both premenopausal and postmenopausal women. There was no suggestion that heavy or long-term smoking increased or decreased risk, nor were there indications that women who began smoking at an early age were at increased risk, as has been hypothesized. The results of this large population-based study indicate that smoking does not influence the risk of breast cancer, even among heavy smokers who began smoking at an early age.

Received 11/3/95; revised 1/23/96; accepted 1/29/96.

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[1] Supported by USPHS Grants CA 47147 and CA 47305.

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Introduction

The effect of cigarette smoking on the risk of breast cancer has remained controversial, despite considerable research. Some recent reports have suggested an increased breast cancer mortality among smokers (1) or an increased risk of breast cancer incidence among heavy smokers who commence the habit at an early age (2). On the other hand, some other studies suggest that cigarette smoking might be inversely related to this malignancy (3), and cigarette smoke exposure seems to protect rats from mammary tumors (4). Although the preponderance of evidence indicates that cigarette smoking has no substantial overall effect on breast cancer risk in humans (3, 5, 6), most studies of the topic did not fully investigate potentially high-risk subgroups such as women who started smoking at an early age or those who were heavy smokers.

To clarify these competing hypotheses, we investigated the relationship between cigarette smoking and breast cancer risk in a very large, population-based case-control study. These data permitted relatively precise investigation of the effects of smoking among individuals at the extremes of exposure: heavy, long-term, or early-life smoking.

Subjects and Methods

This population-based case-control study was conducted in Wisconsin, western Massachusetts, Maine, and New Hampshire, using the cancer registries in those states to identify cases. Methods and some findings from the study have been published previously (7).

Cases were female residents newly diagnosed with invasive breast cancer during the period from April 1988 through December 1991 (for New Hampshire, January 1990 through December 1991). We attempted to contact all cases except those diagnosed more than two years before the registry report or those whose physicians refused permission for contact. Women without a listed telephone number or (if under age 65) a driver's license were also excluded from the study base.

Controls were randomly selected in each state from two sources. Women under age 65 were chosen from state driver's license lists, and those ages 65–74 were selected from among women enrolled in Medicare in the participating states. Computer listings of eligible controls were obtained annually, and controls were chosen randomly to have an age distribution similar to that of the cases, although younger age strata in New England were oversampled to increase statistical power. Women with a history of breast cancer or without a listed telephone were excluded.

Potential subjects were sent a letter describing the study before telephone contact was attempted. Subjects who agreed to participate underwent a telephone interview eliciting information regarding reproductive history, hormone use, personal habits, occupation, a limited number of dietary items, demographic data, and medical history. Included was information regarding the age of initiation of smoking, amount smoked, current smoking status, and time since cessation (among former smokers).

Table 1 Odds ratios for breast cancer by menopausal group and smoking status

Cigarette-smoking status	All subjects[a]		Premenopausal subjects[b]		Postmenopausal subjects[b]	
	Number of controls/cases	Odds ratio (95% CI)[c]	Number of controls/cases	Odds ratio (95% CI)[c]	Number of controls/cases	Odds ratio (95% CI)[c]
Never	4633/3297	1.00	1304/653	1.00	3151/2543	1.00
Former	2635/2010	1.10 (1.01–1.19)	665/411	1.20 (1.01–1.42)	1876/1508	1.04 (0.94–1.14)
Current	2229/1542	1.00 (0.92–1.09)	722/361	0.99 (0.83–1.18)	1400/1108	1.01 (0.90–1.12)

[a] All subjects includes 648 subjects with unknown menopausal status.
[b] P for differences in odds ratios between premenopausal and postmenopausal subjects = 0.20.
[c] Adjusted for age at menarche, age at first term birth, parity, lactation history, family history of breast cancer, history of benign breast disease, alcohol intake, and (all subjects) menopausal status.

Interviewers remained unaware of the case-control status of the subjects for 78% of cases and 90% of controls.

A reference date was used to define exposure status for all study participants. For case subjects, this reference date was the date of diagnosis. For control subjects, it was the date of interview minus the average time interval between diagnosis and interview for cases in the corresponding state. Age was taken to be age at the reference date and parity the number of full-term pregnancies. Subjects were deemed postmenopausal if they reported a natural menopause or a bilateral oophorectomy before the reference date. Women with a history of hysterectomy were considered postmenopausal if their age at the reference date was greater than the 90th percentile for age at natural menopause in the controls (54 years for smokers; 55 years for nonsmokers). Menopausal status was classified as unknown if they had undergone hysterectomy without bilateral oophorectomy and were less than the 90th percentile of age at menopause.

Subjects smoking 1 year before the reference date were considered current smokers; those who had ever smoked a total of 100 or more cigarettes but had stopped smoking by 1 year before the reference date were considered former smokers. (Similar results were obtained if a date of 2 or 3 years before the reference date was used.) Duration of smoking was taken to be the interval between smoking initiation and 1 year before the reference date. Pack-years were computed as the number of cigarettes smoked per day times the duration of smoking in years.

Odds ratios and 95% CIs[3] were used as the measure of association (8). These were calculated by conditional logistic regression using the module Pecan in the statistical package Epicure (Hirosoft International, Seattle, WA). Risk sets were stratified by state and age (in groups of 50, yielding age intervals of about 0.1 year). Multivariate logistic models were used to adjust for potential confounding factors (8). In analyses including all women, these factors were menopausal status (3 categories) age at menarche (4 categories) age at first term birth (5 categories), parity (3 categories), lactation history (3 categories), family history of breast cancer (present or absent), history of benign breast disease (present or absent), and alcohol intake (6 categories). To assess differences between premenopausal and postmenopausal women in effects of risk factors, the significance of interaction terms was investigated in models that included only premenopausal and postmenopausal women. Subjects with missing values for any of the variables in a regression model could not be included in such analyses unless an "unknown" category was incorporated. This was done for history of benign breast disease and family history of breast cancer.

Results

A total of 8,532 eligible cases were identified. Of these, physicians refused contact for 710 (8.3%), 463 (5.4%) were dead at the time of attempted contact, 66 (0.8%) could not be located, 405 (4.7%) refused participation, and 6,888 (81.3%) were interviewed. Of the 11,329 potential controls chosen, 126 (1.1%) were dead, 153 (1.4%) could not be located, 1,521 (13.4%) declined to participate, and 9,529 (84.3%) were interviewed. The basic characteristics of the subjects have been described previously (7).

Overall, 29.4% of cases and 27.8% of controls were former smokers; 22.5% of cases and 23.5% of controls were current smokers (*i.e.*, 1 year before the reference date). Women currently smoking cigarettes had a breast cancer risk similar to that of those who were never smokers both overall and among premenopausal and postmenopausal women separately. Overall, the odds ratio was 1.00 (95% CI, 0.92–1.09; Table 1). There was also no substantial increase in risk among former smokers, although in this large data set the overall odds ratio of 1.10 was statistically different from 1.00 (95% CI, 1.01–1.19). For premenopausal women, the odds ratio for former smokers was 1.20 (95% CI, 1.01–1.42), and for postmenopausal women it was 1.04 (95% CI, 0.94–1.14); the differences in these odds ratios were compatible with chance (P = 0.28)

The number of cigarettes usually smoked per day was unrelated to breast cancer risk (Table 2). Very heavy smokers (more than 2 packs/day) had an odds ratio of 1.09 (95% CI, 0.79–1.49). Duration of smoking was also unassociated with risk; women who had smoked cigarettes for more than 50 years had an odds ratio of 1.07 (95% CI, 0.84–1.37). Breast cancer risk was also not related to duration of smoking among heavy smokers (more than 2 packs/day), to amount smoked among long-term smokers (more than 20 years), or to pack-years of smoking (data not shown).

Because of the slightly elevated relative risk among former smokers, we investigated the association between risk and time since cessation of smoking (Table 3). For premenopausal women (among whom the associations of risk with former smoking were most noticeable), there was no pattern of risk in relation to time since cessation. In contrast, among postmenopausal former smokers, risk diminished steadily with time since last smoked. The odds ratio was 1.41 (95% CI, 1.12–1.78) for cessation within 3 years of the reference date, and fell to 0.90 (95% CI, 0.73–1.10) after 30 years of cessation. However, the linear trends in risk with time since last smoked were not statistically different in premenopausal and postmenopausal women (P = 0.21).

[3] The abbreviation used is: CI, confidence interval.

Table 2 Odds ratios for breast cancer by amount smoked and duration of smoking

	All subjects[a]		Premenopausal subjects, odds ratio (95% CI)[b]	Postmenopausal subjects, odds ratio (95% CI)[b]
	Number of controls/cases	Odds ratio (95% CI)[b]		
Number of cigarettes smoked/day				
Never smoker	4633/3297	1.00	1.00	1.00
≤10	1759/1313	1.04 (0.95–1.14)	1.18 (0.98–1.42)	0.97 (0.87–1.09)
10, ≤20	2066/1492	1.07 (0.98–1.17)	1.06 (0.87–1.27)	1.06 (0.95–1.17)
>20, ≤30	463/350	1.06 (0.90–1.24)	0.95 (0.70–1.31)	1.06 (0.87–1.28)
>30, ≤40	394/276	1.04 (0.87–1.24)	1.12 (0.81–1.55)[c]	1.05 (0.87–1.26)[c]
>40	115/79	1.09 (0.79–1.49)		
Linear trend/10 cigarettes		0.99 (0.96–1.04)	0.96 (0.88–1.04)[d]	1.01 (0.97–1.06)[d]
Duration of smoking, years				
Never smoker	4633/3297	1.00	1.00	1.00
≤10	710/421	0.96 (0.83 –1.10)	1.12 (0.90 –1.40)	0.88 (0.72 –1.07)
>10, ≤20	923/584	1.02 (0.90 –1.15)	1.13 (0.93 –1.38)	0.89 (0.74 –1.06)
>20, ≤30	1149/872	1.12 (1.00 –1.25)	1.01 (0.83 –1.24)	1.12 (0.97 –1.29)
>30, ≤40	1076/873	1.12 (1.00 –1.25)	1.28 (0.88 –1.85)[e]	1.09 (0.96 –1.23)
>40, ≤50	797/609	1.01 (0.89 –1.15)		0.99 (0.87 –1.13)
>50	197/180	1.07 (0.84 –1.37)		1.05 (0.82 –1.35)
Linear trend/10 years		1.03 (0.99 –1.08)	0.93 (0.82 –1.05)[d]	1.04 (0.99 –1.09)[d]

[a] All subjects includes 648 subjects with unknown menopausal status.
[b] Adjusted for age at menarche, age at first term birth, parity, lactation history, family history of breast cancer, history of benign breast disease, alcohol intake, and (all subjects) menopausal status.
[c] Estimates for >30 cigarettes smoked/day.
[d] *P* for differences in linear trend between premenopausal and postmenopausal ever smokers = 0.27 for amount smoked, 0.84 for duration smoked.
[e] Estimate for >30 years smoked.

Table 3 Odds ratios for breast cancer in relation to time since cessation of smoking

Years since cessation	All subjects[a]		Premenopausal subjects, odds ratio (95% CI)[b]	Postmenopausal subjects, odds ratio (95% CI)[b]
	Number of controls/cases	Odds ratio (95% CI)[b]		
Never smoker	4633/3297	1.00	1.00	1.00
≤3	266/249	1.39 (1.14 –1.68)	0.98 (0.65 –1.49)	1.41 (1.12 –1.78)
>3, ≤10	714/580	1.23 (1.08 –1.40)	1.38 (1.07 –1.78)	1.10 (0.94 –1.30)
>10, ≤20	818/610	1.08 (0.95 –1.20)	1.17 (0.91 –1.49)	1.03 (0.88 –1.19)
>20, ≤30	533/363	0.94 (0.81 –1.10)	1.13 (0.80 –1.60)[c]	0.91 (0.76 –1.08)
>30	304/208	0.92 (0.75 –1.12)		0.90 (0.73 –1.10)
Linear trend/10 years[d]		0.91 (0.85 –0.96)	1.08 (0.88 –1.34)[e]	0.91 (0.85 –0.97)[e]

[a] All subjects includes 648 subjects with unknown menopausal status.
[b] Adjusted for age at menarche, age at first term birth, parity, lactation history, family history of breast cancer, history of benign breast disease, alcohol intake, and (all subjects) menopausal status.
[c] Estimate for >20 years since cessation.
[d] Among former smokers only.
[e] *P* for differences in linear trend between premenopausal and postmenopausal former smokers = 0.15.

There was no overall relationship between age at initiation of smoking and breast cancer risk (Table 4). Women who began smoking at an early age (before 15 years old) were not at materially increased risk, with an odds ratio of 1.13 (95% CI, 0.97–1.31). Restricting this analysis to those who usually smoked more than 20 cigarettes/day left these findings unchanged (odds ratio for starting smoking before age 15, 1.04; 95% CI, 0.81–1.33). Among premenopausal heavy smokers, there was an apparent linear trend of lower risk with later age of smoking initiation, but this was the result of lower risks at later ages, not a higher risk for those who began early.

There was no evidence of an effect of smoking concentrated within subgroups of the study population. Odds ratios for current and former smokers within high and low categories of the covariates used in the multivariate models were all close to 1.0 (data not shown).

Discussion

In this large, population-based study of breast cancer, we found little evidence that cigarette smoking either increases or decreases breast cancer risk. Early age at smoking initiation was not associated with an altered risk, nor was heavy smoking or long-term smoking.

Previous studies of the relationship between cigarette smoking and the risk of breast cancer have not been entirely consistent. A few studies have suggested an inverse association between smoking and risk (9, 10), findings that have been ascribed to biases in control selection (11) or chance variation. Some other reports have provided indications of an increased incidence of breast cancer among smokers, particularly for premenopausal women or heavier smokers (12–15). Many of these studies were small, however, or also involved potential biases (11). Former smokers have been noted to have an increased risk in several other studies (15–17), although most

Table 4 Odds ratios for breast cancer in relation to age at smoking initiation

Age started smoking	All subjects[a]		Premenopausal subjects, odds ratio (95% CI)[b]	Postmenopausal subjects, odds ratio (95% CI)[b]
	No. of controls/cases	Odds ratio (95% CI)[b]		
All subjects				
Never smoker	4633/3297	1.00	1.00	1.00
≤15 years	637/405	1.13 (0.97–1.31)	1.06 (0.82–1.36)	1.17 (0.96–1.43)
>15, ≤18 years	1918/1386	1.09 (0.99–1.19)	1.10 (0.92–1.32)	1.04 (0.93–1.16)
>18, ≤21 years	1143/868	1.05 (0.94–1.17)	1.09 (0.87–1.36)	1.04 (0.91–1.18)
>21, ≤24 years	395/328	1.09 (0.92–1.29)	1.39 (0.94–2.06)	1.01 (0.84–1.23)
>24, ≤27 years	297/208	0.89 (0.73–1.09)	0.93 (0.62–1.38)[c]	0.85 (0.68–1.06)
>27 years	453/344	0.96 (0.82–1.13)		0.98 (0.83–1.17)
Linear trend/5 years		0.98 (0.94–1.02)	0.95 (0.83–1.09)[e]	0.99 (0.94–1.03)[e]
Heavy smokers (>20 cigarettes/day)				
Never smoker		1.00	1.00	1.00
≤15 years	201/135	1.04 (0.81–1.33)	1.04 (0.66–1.63)	1.05 (0.75–1.47)
>15, ≤18 years	402/296	1.15 (0.97–1.37)	1.18 (0.84–1.65)	1.12 (0.91–1.39)
>18, ≤21 years	190/151	1.08 (0.85–1.37)	0.77 (0.49–1.19)[d]	1.17 (0.88–1.55)
>21 years	178/122	0.87 (0.67–1.12)		0.87 (0.66–1.16)
Linear trend/5 years		0.98 (0.86–1.11)	0.68 (0.45–1.04)[e]	1.04 (0.91–1.19)[e]

[a] All subjects includes 648 subjects with unknown menopausal status.
[b] Adjusted for age at first term birth, parity, lactation history, family history of breast cancer, history of benign breast disease, alcohol intake, and (all subjects) menopausal status.
[c] Estimate for age >24 years.
[d] Estimate for age >18 years.
[e] P for differences in trend between premenopausal and postmenopausal subjects = 0.81 for all ever smokers, and 0.20 for ever heavy smokers.

investigations have not found a materially increased or decreased risk after smoking cessation. Indeed, most previous studies have noted that cigarette smokers in general are not at substantially altered risk of breast cancer incidence compared to nonsmokers (3, 5, 6), conclusions that agree with our findings.

Nonetheless, the large American Cancer Society cohort analysis reported that women who smoked cigarettes had a modestly higher breast cancer mortality than nonsmokers (adjusted mortality ratio of 1.3; Ref. 1). There were trends of increasing mortality with amount and duration of smoking, and an apparent (statistically nonsignificant) trend of increased risk of breast cancer death with early initiation of the habit. These findings are compatible with ours, under the assumption that smoking is associated with the prognosis of breast cancer but not its incidence. For example, smokers may present at a later stage, or the cardiopulmonary disease associated with smoking may lead to increased breast cancer mortality. There is some evidence that at diagnosis smokers have more advanced breast cancer (18) and colorectal cancer (19), but it is not clear what underlies these associations.

Another recent analysis reported an increased breast cancer incidence among heavy smokers who began smoking at an early age (less than 16 years old; Ref. 2). However, other studies (like ours) that investigated the impact of age of smoking initiation found no association, either among heavy smokers (20), or overall (16, 21–25). Thus, in aggregate, there appears to be no association of early smoking with breast cancer risk, even among heavy smokers.

There are conflicting hypotheses regarding the possible effects of smoking on breast cancer risk. On the one hand, there are several reasons why cigarette smoking might be expected to increase breast cancer risk. Smoking has been associated with an elevated cancer risk at many sites remote from direct smoke contact, and nipple aspirates of smokers are more mutagenic than those of nonsmokers (26). Nicotine is found in breast fluid of smokers (27, 28), and presumably other carcinogenic smoke constituents are absorbed into the breast as well. On the other hand, several considerations suggest that smokers might have a lower risk of breast cancer than nonsmokers. Smoking is associated with an earlier menopause and a lower body weight (3), effects that probably would reduce the risk of postmenopausal breast cancer, albeit only modestly (17). Moreover, the "antiestrogenic" effect of smoking might be expected to decrease the risk of breast cancer, as it apparently does for endometrial cancer, particularly among postmenopausal women (3). Finally, rats exposed to cigarette smoke seem to have fewer mammary tumors than do controls (4).

It is also possible both these hypotheses are correct, if a carcinogenic effect of smoking is counterbalanced by a protective hormonal effect, leaving no net impact on risk. This combination of effects is compatible with our findings regarding the increase in risk for recent postmenopausal quitters. Here, with the removal of the suppressive effect of the smoking, longer-lasting carcinogenic effects would be left to dominate. However, in view of the many comparisons made in our analysis, it seems most reasonable to ascribe this solitary finding to chance.

Our study has several major strengths. The large sample size permitted us to estimate the effects of extremes of exposure with considerable precision. Moreover, the population-based design of the study, together with a high response rate, makes major response biases unlikely. Substantial confounding in the data is unlikely: the relative risk estimates presented were adjusted for major known breast cancer risk factors, with little change over those obtained from the matching by age and state. A potential weakness is that in our case-control design, the responses of the cases could have been affected by their experience with the disease. However, because there is no strong public view that smoking should be related to breast cancer, such a response bias seems unlikely. Also, our questionnaire did not include items regarding passive smoking, but in the absence of an effect of active smoking, a major impact of such smaller exposures is implausible (25).

Overall, our results provide no support for either a protective effect of smoking on breast cancer risk or an increase in

risk among smokers, even in subgroups such as those who began smoking early in life or who smoke heavily. Despite *a priori* considerations, smokers appear to have an unaltered risk of breast cancer in comparison with nonsmokers. However, smoking could still exert an adverse impact on breast cancer if it led to decreased survival among cases.

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